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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/00	A1	(11) International Publication Number: WO 96/23486 (43) International Publication Date: 8 August 1996 (08.08.96)
(21) International Application Number: PCT/US96/00577 (22) International Filing Date: 16 January 1996 (16.01.96) (30) Priority Data: 08/380,540 30 January 1995 (30.01.95) US (71) Applicant (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): POPLI, Shankar, Dass [-/US]; 31 Pelham Road, Marlton, NJ 08053 (US). GO, Zenaida, Ong [-/US]; Apartment #20, 360 Valley Avenue, Hammononton, NJ 08037 (US). (74) Agents: FLYNN, Steven, H.; American Home Products Corporation, Five Giralda Farms, Madison, NJ 07940 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: TASTE MASKING LIQUIDS (57) Abstract There is provided a pharmaceutically acceptable taste masking liquid excipient base for administration of relatively large amounts of unpleasant tasting medicines, said excipient base having higher than normal viscosities due to a combination of polyethylene glycol and cellulosic material.		

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TASTE MASKING LIQUIDS**BRIEF DESCRIPTION OF THE INVENTION**

The present invention is directed to a pharmaceutically acceptable taste masking liquid excipient base for administration of a relatively large amount of unpleasant tasting medicines. More particularly, the taste masking effect is produced by increasing the viscosity of the liquid excipient base by adding to the liquid excipient base a viscosity increasing amount of a combination of a normally solid polyethylene glycol and sodium carboxymethyl cellulose.

The invention is further directed to medicinal compositions comprising the claimed liquid excipient base and said unpleasant tasting medicines.

Still further, the invention is directed to a method for taste masking unpleasant tasting medicines through their incorporation into the claimed liquid excipient bases.

BACKGROUND OF THE INVENTION

Pharmaceutically acceptable liquid excipient bases for administration of unpleasant tasting medicines are well known in the art. A typical system is described in United States Letters Patent No. 5,260,073 to Roger J. Phipps at column 7 as including a medicine, a solvent, a co-solvent, a buffer, a surfactant, a preservative, a sweetening agent, a flavoring agent, a dye or pigment, a viscosity modifier and water. The patent provides several examples of each ingredient in the system.

Although liquid excipient bases and their many ingredients are well known, unpleasant tasting medicines alone or in combination still present challenges to one skilled in the art to provide better taste masked products and, in certain instances, to provide taste masking for higher dosage amounts of unpleasant tasting medicines in smaller amounts of vehicle.

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SUMMARY OF THE INVENTION

The present invention provides a pharmaceutically acceptable taste masking liquid excipient base for administration of relatively large amounts of unpleasant tasting pharmaceutically active compounds which liquid excipient base comprises polyethylene glycol having a molecular weight of at least 1000 and a cellulosic material, the spindle viscosity of the excipient base being between about 150 and about 1000 centipoises at 50 RPM.

The invention further provides pharmaceutically acceptable taste masking liquid excipient bases for administration of relatively large amounts of unpleasant tasting pharmaceutically active compounds.

Surprisingly, it has been found that the high viscosity liquid excipient base provides taste masking benefits to the extent that even extra strength formulations containing increased concentrations of adverse tasting pharmaceutically active compounds can be prepared. For example, guaifenesin, normally administered in dosages of no more than 100 milligrams in 5 milliliters of liquid, may be administered in dosages of 200 milligrams in the same volume of liquid without the patient experiencing an unduly adverse taste.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutically acceptable taste masking bases useful in this invention are those having incorporated therein per 100 milliliters of liquid base about 5 to about 20 grams, preferably about 10 to about 15 grams, of polyethylene glycol having an average molecular weight of about 950 to about 2200, preferably about 1400 to about 1600, and a cellulosic material, the weight ratio of polyethylene glycol to the cellulosic material being between about 100:1 and about 20:1, such that the spindle viscosity is between about 150 and about 1000 centipoises at 50 RPM. These bases typically possess a spindle viscosity of about 150 to about 1200 centipoises when measured at 10 RPM. The higher

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viscosities of these bases are preferred for certain applications since such liquids are easier to pour from glass bottles and do not tend to spill from a spoon during their administration, especially to children.

The pH of the liquid base is from about 2.5 to about 5. At a lower pH, the cellulosic may tend to crystalize out, and at a higher pH, the taste worsens and preservatives must be used.

The polyethylene glycol useful in the practice of the present invention are those having an average molecular weight of about 950 to about 2200. Preferably, the polyethylene glycol has an average molecular weight of about 1400 to about 1600. Most preferably, the polyethylene glycol used in the practice of the present invention has an average molecular weight of about 1450. The use of mixtures of such polyethylene glycols is further within the practice of the present invention. As stated above, the polyethylene glycol component is used in amount of about 5 to about 20 grams, preferably about 10 to about 15 grams, per 100 milliliters of the liquid excipient base. The polyethylene glycol used in the specific examples was Polyethylene Glycol 1450 N.F. This polyethylene glycol, having a molecular weight of 1450 can be obtained from a number of suppliers. For instance, it is sold by Union Carbide Chemicals and Plastic Company, Inc. of Danbury, CT as CARBOWAX® 1450® and by Dow Chemical Company of Midland, Michigan as Dow Polyglycol E1450.

The cellulosic materials useful in the practice of the present invention are food grade materials and include methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose and mixtures thereof. Also useful are salts of such materials, such as the sodium salt of carboxymethyl cellulose, typically produced through the sodium hydroxide neutralization of a carboxylic acid derivative of cellulose.

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Preferred is the use of such sodium salt of carboxymethyl cellulose. As stated above, such materials are used in amounts such that (a) the ratio of polyethylene glycol:cellulosic material is between about 100:1 and about 20:1, and (b) the spindle viscosity of the liquid excipient bases is between about 150 and about 1000 centipoise at 50 RPM. In a preferred embodiment of the present invention wherein the cellulosic material is the sodium salt of carboxymethylcellulose, such material is present in amounts between about 0.05 and about 0.6 grams, preferably between about 0.1 and about 0.5 grams, per 100 milliliters of the liquid excipient bases.

The cellulosic material used in the specific examples was HERCULES® Cellulose Gum 7MF which is the sodium salt of carboxymethylcellulose with a minimum purity of 99.5%, food grade, with a Type 7 Degree of Substitution and a medium viscosity range of 400-800 cps as a 2% by weight in water solution. The pharmaceutically active compounds and excipients other than the polyethylene glycol and the sodium carboxymethyl cellulose were of U.S.P. grade.

The pharmaceutically active compounds useful in the practice of the present invention include antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesic drugs such as acetaminophen and phenacetin. These materials are incorporated into the claimed liquid excipient base in amounts governed by the solubility of the material in such excipient base and such that conventional dosages thereof shall be in compliance with applicable FDA regulations. For example, materials highly soluble in the liquid excipient base must not be incorporated to the extent that a typical dose (such as one teaspoon) contains more of such material than permitted by such regulations.

Among the antihistamines useful in the practice of the present invention (along with their preferred salt form) are chlorpheniramine (maleate), brompheniramine (maleate),

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dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine (HCl), diphenhydramine (HCl), doxylamine (succinate), tripeleminamine (HCl), cyproheptadine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrrolamine (maleate, tannate) and azatadine (maleate).

The antitussives useful in the practice of the present invention (along with their preferred salt form) are caramiphen (edisylate), dextromethorphan (HBr) and codeine (phosphate, sulfate).

The decongestants useful in the practice of the present invention (along with their preferred salt form) are pseudoephedrine (HCl), phenylpropanolamine (HCl) and phenylephrine (bitartrate, tannate, HBr, HCl). Phenylpropanolamine (HCl) has been found to be unsuitable for use in the present invention if high fructose corn syrup sweetener is present. Therefore, if phenylpropanolamine HCl is used in conjunction with a sweetener, a sweetener such as sorbitol should be employed.

The expectorants useful in the practice of the present invention (along with their preferred salt form) are terpin hydrate, guaifenesin (glyceryl guaiacolate), potassium (iodide, citrate) and potassium guaicol sulfonate.

The non-steroidal anti-inflammatory drugs (NSAIDs) for use in the practice of the present invention may be selected from any of the following categories:

- (1) propionic acid derivatives;
- (2) acetic acid derivatives;
- (3) fenamic acid derivatives;
- (4) biphenylcarboxylic acid derivatives; and
- (5) oxicams.

Of the propionic acid derivatives for use herein, ibuprofen, naproxen, ketoprofen, flurbiprofen, fenoprofen, suprofen, fenbufen, and fluprofen may be mentioned as preferred compounds.

Of the acetic acid derivatives for use herein, tolmetin sodium, zomepirac, sulindac and indomethacin are included.

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Of the fenamic acid derivatives for use herein, mefenamic acid and meclofenamate sodium are included.

Di flunisal and flufenisal are biphenylcarboxylic acid derivatives.

The oxicams include piroxicam, sudoxicam and isoxicam.

Of course, it will be appreciated by those skilled in the art, that any of the foregoing compounds may be utilized in the form of their pharmaceutically acceptable salt forms, e.g. $-\text{COO}^-\text{Na}^+$, $-\text{COO}^-\text{K}^+$, and the like.

Of the foregoing NSAIDs, ibuprofen and naproxen are the most preferred.

Other analgesic compounds useful in the practice of the present invention include acetaminophen and phenacetin.

Of the pharmaceutically active compounds described above, those which are particularly preferred are set forth below along with preferred ranges for their inclusion into the claimed liquid excipient base.

Guaifenesin may be present in amount of up to 300 milligrams per 5 mls. of the excipient base. Preferably, guaifenesin is present in amounts of about 10 to about 300 milligrams per 5 mls. of the excipient base. Most preferably, guaifenesin is present in amounts of about 100 to about 200 milligrams per 5 mls. of the excipient base.

Dextromethorphan may be present in amounts of between about 5 and about 20 milligrams per 5 mls. of the excipient base. Most preferably, dextromethorphan is present in amounts of about 10 to about 15 milligrams per 5 mls. of the excipient base.

Brompheniramine may be present in amount of between about 0.5 and about 4.0 milligrams per 5 mls. of the excipient base. Most preferably, brompheniramine is present in amounts of about 2.0 milligrams per 5 mls. of the excipient base.

Pseudoephedrine may be present in amount of between about 10 and about 60 milligrams per 5 mls. of the excipient

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base. Most preferably, pseudoephedrine is present in amounts of about 15 to about 30 milligrams per 5 mls. of the excipient base.

Acetaminophen may be present in amounts of up to about 200 milligrams per 5 mls. of the excipient base. Preferably, acetaminophen is present in amounts of about 50 to about 200 milligrams per 5 mls. of the excipient base. Most preferably, acetaminophen is present in amounts of about 150 to about 175 milligrams per 5 mls. of the excipient base.

Ibuprofen may be present in amounts of up to about 150 milligrams per 5 mls. of the excipient base. Preferably it is present in amounts of between about 50 and about 150 milligrams per 5 mls. of the excipient base. Most preferably, ibuprofen is present in amounts of about 100 milligrams per 5 mls. of the excipient base.

Naproxen may be present in amounts of about 50 to about 250 milligrams per 5 mls. of the excipient base. Preferably, it is present in amounts of between about 100 and about 150 milligrams per 5 mls. of the excipient base.

Excipients other than the polyethylene glycol and the sodium carboxymethyl cellulose useful in the practice of the present invention are those known to the art. These include humectants such as glycerin and propylene glycol, preservatives such sodium benzoate and paraben, sweeteners such as sodium saccharin, corn syrup and sorbitol solutions, menthol and various flavoring and coloring agents.

Although not willing to be bound thereby, it is believed that normally solid polyethylene glycol when melted and mixed with the propylene glycol, serves to solubilize the active ingredient and inhibits its crystallization at room temperature.

The invention will now be described with respect to following specific examples.

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Example 1

The formulation of the invention set forth below was prepared in accordance with the following procedure. The example illustrates a formulation containing 200 milligrams of guaifenesin per 5 ml of formulation, double the normal amount, which has an acceptable taste.

INGREDIENTS	AMT/5ML	%	AMT/50 0 ML
GUAIFENESIN, USP	200.0 MG	4.0	20.0g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.20	1.0g
PSEUDOEPHEDRINE HCl, USP	30.00 MG	0.60	3.0g
POLYETHYLENE GLYCOL 1450, NF	500.00 MG	10.00	50.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	75 ml
GLYCERIN, USP	0.25 ML	5.00	25 ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.00	2 25ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	25ml
L-MENTHOL, USP	1.20 MG	0.024	0.12g
CITRIC ACID ANHYDROUS, USP	45.00 MG	0.90	4.5g
SODIUM BENZOATE, USP	5.00 MG	0.10	0.5g
SACCHARIN SODIUM, USP	35.00 MG	0.70	3.5g
COLORING AND SWEETENER	5.15 MG	0.103	0.515g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	25.00 MG	0.50	2.5g
ART. FRUIT FLAVORS	0.036 ML	0.72	3.6 ml
PURIFIED WATER, USP QS TO	5.00 ML	100.0	500 ml

The PEG 1450 was introduced into a flask and melted at 50°-60°C and 62.5 ml of propyleneglycol was added with stirring. The guaifenesin, the dextromethorphan HBr and the pseudoephedrine HCl were then dissolved in the mixture. In a separate flask, the sodium CMC was dispersed in glycerin, and in a third flask, the sodium benzoate and sodium saccharin were dissolved in 60ml of purified water. The sodium CMC dispersion was added to the third flask and

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stirred for at least 30 minutes or until the preparation becomes thick. The thick preparation was added to the bottle in the first flask. To the first flask were then added the sorbitol solution and the corn syrup with continuous stirring. The menthol was then dissolved in 12.5 ml of propylene glycol and added to the bulk. The citric acid was dissolved in 10 ml water and added to the bulk. The flavors and coloring were added and then purified water to 500 ml.

The resulting formulation has a pH of 3.38, 3.40, a spindle #3 viscosity at 10 RPM of 590 c.p.s. and a spindle viscosity at 50 rpm of 534 cps. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 20:1.

The formulation has an acceptable flavor and taste.

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Example 2

The formulation of this example has the same proportions medicines and polyethyleneglycol as in the previous example but only one fifth as much sodium CMC.

INGREDIENTS	AMT/5ML	%	AMT/1.0 L
GUAIFENESIN, USP	200.0 MG	4.0	40.0g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.20	2.0g
PSEUDOEPHEDRINE HCl, USP	30.00 MG	0.60	6.0g
POLYETHYLENE GLYCOL 1450, NF	500.00 MG	10.00	100.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	150.0ml
GLYCERIN, USP	0.25 ML	5.00	50.0ml
HIGH FRUCTOSE CORN SYRUP 85	2.25 ML	45.00	450.0ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	50.0ml
L-MENTHOL, USP	1.20 MG	0.024	0.24g
CITRIC ACID ANHYDROUS, USP	25.00 MG	0.5	5.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	1.5g
SACCHARIN SODIUM, USP	35.00 MG	0.70	7.0g
COLORING AND SWEETENER	5.5 MG	0.11	1.1g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	5.00 MG	0.1	1.0g
ARTIFICIAL FRUIT FLAVOR	0.003 ML	0.06	0.6ml
PURIFIED WATER, USP QS TO			1L

The procedure for this formulation was essentially the same as in the previous example except that the pseudoephedrine HCl was added with the citric acid dissolved in water and the coloring was separately added dissolved in water.

The resulting formulation had a pH of 3.509, a spindle #1 viscosity at 10 RPM of 236-256 cps and a spindle viscosity of 243-248 cps at 20 RPM. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 100:1.

The formulation had an acceptable taste.

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Example 3

In this formulation only two medicines, guaifenesin and dextromethorpan HBr are used.

INGREDIENTS	AMT/5ML	%	AMT/1.0 L
GUAIFENESIN, USP	200.0 MG	4.0	40.0g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.20	2.0g
POLYETHYLENE GLYCOL 1450, NF	500.00 MG	10.00	100.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	150.0ml
GLYCERIN, USP	0.25 ML	5.00	50.0ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.00	450.0ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	50.0ml
L-MENTHOL, USP	1.20 ML	0.024	0.24g
CITRIC ACID ANHYDROUS, USP	30.0 MG	0.6	6.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	1.5g
SACCHARIN SODIUM, USP	28.0 MG	0.56	5.6g
COLORING AND SWEETENER	5.5 MG	0.11	1.1g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	5.0 MG	0.1	1.0g
ART. FLAVORS	0.003 ML	0.06	0.6ml
PURIFIED WATER, USP QS TO	5.00 ML	100.0	1.0L

The procedure for this formulation was essentially the same as in Example 2.

The resulting formulation has a pH of 3.45, 3.51, a spindle #1 viscosity at 10 RPM of 177 cps and a spindle viscosity at 20 RPM of 178 cps. which rose to 210 cps at both 10 RPM and 20 RPM within 24 hours. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 100:1.

The formulation had an acceptable taste.

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Example 4

This formulation was similar to Example 2, except that the guaifenesin was 100 milligrams and the PEG content was 350 milligrams and shows that the PEG content must be coordinated with the sodium CMC content to achieve the proper viscosity.

INGREDIENTS	AMT/5ML	%	AMT/1.0 L
GUAIFENESIN, USP	100.0 MG	2.0	200g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.20	2.0g
POLYETHYLENE GLYCOL 1450, NF	350.0 MG	7.00	70.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	150.0ml
GLYCERIN, USP	0.25 ML	5.00	50.0ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.00	450.0ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	50.0ml
MENTHOL, USP	1.20 ML	0.024	0.24g
CITRIC ACID ANHYDROUS, USP	25 MG	0.5	5.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	1.5g
SACCHARIN SODIUM, USP	35.0 MG	0.7	7.0g
COLORING AND SWEETENER	5.5 MG	0.11	1.1g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	5.0 MG	0.1	1.0g
ART. FLAVORS	0.003 ML	0.06	0.6ml
PURIFIED WATER, USP QS TO			1 L
PSEUDOEPHEDRINE HCL, USP	30.0 MG	0.60	6.0g

The procedure for this formulation was essentially the same as in the previous example except that the pseudoephedrin was dissolved with citric acid in water.

The resulting formulation had a pH of 3.40, a spindle #1 viscosity at 10 RPM of 101 cps and a spindle #1 viscosity at 20 RPM of 102 cps. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 70:1.

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Example 5

In this formulation similar to Example 2 only 100 milligrams of guaifenesin was employed, the polyethylene glycol was reduced to 350 milligrams and the sodium CMC was increased to 12.5 milligrams.

INGREDIENTS	AMT/5ML	%	AMT/1.0 L
GUAIFENESIN, USP	100.0 MG	2.0	20.0g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.20	2.0g
POLYETHYLENE GLYCOL 1450, NF	350.00 MG	7.00	70.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	150.0ml
GLYCERIN, USP	0.25 ML	5.00	50.0ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.00	450.0ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	50.0ml
L-MENTHOL, USP	1.20 ML	0.024	0.24g
CITRIC ACID ANHYDROUS, USP	25 MG	0.5	5.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	1.5g
SACCHARIN SODIUM, USP	35.0 MG	0.7	7.0g
COLORING AND SWEETENER	5.5 MG	0.11	1.1g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	12.5 MG	0.25	2.5g
ART. FLAVORS	0.003	0.06	0.6ml
PURIFIED WATER, USP QS TO			1 L
PSEUDOEPHEDRINE HCL, USP	30.0 MG	0.60	6.0g

The procedure for this formulation was essentially the same as Example 4.

The resulting formulation has a pH of 3.49, a spindle #1 viscosity at 10 RPM of 176 cps and a spindle viscosity at 20 RPM of 174 cps. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 28:1.

The formulation had an acceptable taste.

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Example 6

In this experiment, the amount of guaifenesin was increased to 200 milligrams per 5 milliliters and the amount of the other ingredients remain the same as in this Example 5. The pH of the resulting formulation was 3.63 and the spindle #1 viscosity was 363 cps at 10 RPM and 357 cps at 20 RPM. The taste of the formulation was acceptable.

Example 7

In this formulation similar to Example 3 only 100 milligrams of guaifenesin were employed, the polyethylene glycol was reduced to 350 milligrams and the sodium CMC was increased to 12.5 milligrams.

INGREDIENTS	AMT/5ML	%	AMT/1.0 L
GUAIFENESIN, USP	100 MG	2.0	20.0g
DEXTROMETHORPHAN HBR, USP	10.0 MG	0.2	2.0g
POLYETHYLENE GLYCOL 1450, NF	350 MG	7.0	70.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.0	150.0ml
GLYCERIN, USP	0.25 ML	5.0	50.0ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.0	450ml
SORBITOL SOLUTION, USP	0.25 ML	5.0	50ml
L-MENTHOL, USP	1.20 ML	0.024	0.24g
CITRIC ACID ANHYDROUS, USP	30.0 MG	0.6	6.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	1.5g
SACCHARIN SODIUM, USP	28.0 MG	0.56	5.6g
COLORING AND SWEETENER	5.5 MG	0.11	1.1g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	12.5 MG	0.25	2.5g
FLAVORS	0.003 ML	0.06	0.6ml
PURIFIED WATER, USP QS TO			1 L

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The procedure for this formulation was essentially the same as in Example 3.

The resulting formulation has a pH of 3.45, a spindle #1 viscosity at 10 RPM of 202 cps and a spindle viscosity at 20 RPM of 197 cps. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 28:1.

The formulation has an acceptable taste.

Example 8

In this formulation, acetaminophen is present as the pharmaceutically active compound.

INGREDIENTS	AMT/5ML	%	AMT/0.5 L
ACETAMINOPHEN, USP	160.0 MG	3.2	40.0g
POLYETHYLENE GLYCOL 1450, NF	500.00 MG	10.00	50.0g
PROPYLENE GLYCOL, USP	0.75 ML	15.00	75.0ml
GLYCERIN, USP	0.25 ML	5.00	25.0ml
HIGH FRUCTOSE CORN SYRUP 95	2.25 ML	45.00	225.0ml
SORBITOL SOLUTION, USP	0.25 ML	5.00	25.0ml
L-MENTHOL, USP	1.20 ML	0.024	0.12g
CITRIC ACID ANHYDROUS, USP	30.0 MG	0.6	3.0g
SODIUM BENZOATE, USP	7.5 MG	0.15	0.75g
SACCHARIN SODIUM, USP	28.0 MG	0.56	2.8g
COLORING AND SWEETENER	5.5 MG	0.11	0.55g
SODIUM CARBOXYMETHYLCELLULOSE 7MF, USP	5.0 MG	0.1	0.5g
PURIFIED WATER, USP QS TO			500 ML

The PEG 1450 was introduced into a flask and melted at 50°-60°C and 60 ml. of the propylene glycol was added with stirring. The acetaminophen was then added and dissolved in the mixture. In a separate flask, the sodium CMC was dispersed in glycerin, and in a third flask, the sodium

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third flask and stirred for about 45 minutes or until the preparation became thick. The thick preparation was added to the bottle in the first flask (containing the acetaminophen). To the first flask were then added the sorbitol solution and the corn syrup with continuous stirring. The menthol was then dissolved in 15.0 ml of propylene glycol and added to the bulk. The sweetener and coloring were added and then purified water added until the volume of the solution equaled 500 ml. Citric acid dissolved in 10 ml water was then added to the bulk until the pH was about 3.5.

The resulting formulation has a pH of 3.48 3.56, a spindle #3 viscosity at 10 RPM of 234 c.p.s. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 100:1.

The formulation has an acceptable flavor and taste.

Example 9

The procedure of Example 8 was repeated except that 20.0 grams of acetaminophen were used. This produced a composition containing 200 mg of acetaminophen per 5 ml of the composition.

The resulting formulation has a pH of 3.45 3.51, a spindle #3 viscosity at 10 RPM of 256 c.p.s. The ratio of polyethylene glycol to sodium carboxymethylcellulose is 100:1.

The formulation has an acceptable flavor and taste.

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Claims:

1. A pharmaceutically acceptable taste masking liquid excipient base for administration of relatively large amounts of unpleasant tasting pharmaceutically active compounds which liquid excipient base comprises (a) polyethylene glycol having a molecular weight of about 950 to about 2200, and (b) a cellulosic compound, the spindle viscosity of the liquid excipient bases being between about 150 and about 1000 centipoises at 50 RPM and 150-1200 centipoises at 10 RPM.
2. The excipient base of Claim 1 wherein the polyethylene glycol has a molecular weight of between 1400 and about 1600.
3. The excipient base of Claim 1 wherein the weight ratio of polyethylene glycol and cellulosic compound is between about 100:1 and about 20:1.
4. The excipient base of Claim 1 wherein the cellulosic compound is selected from the group consisting of methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, mixtures and salts thereof
5. The excipient base of Claim 1 wherein the cellulosic compound is sodium carboxymethyl cellulose.
6. The excipient base of Claim 5 wherein the weight ratio of polyethylene glycol and sodium carboxymethylcellulose is between about 100:1 and about 20:1.
7. The excipient base of Claim 1 having a pH of between about 2.5 and about 5.

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8. A pharmaceutical composition comprising (i) a liquid excipient base comprising (a) polyethylene glycol having a molecular weight of about 950 to about 2200, and (b) a cellulosic compound selected from the group consisting of methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, mixtures and salts thereof, the spindle viscosity of the liquid excipient bases being between about 150 and about 1000 centipoises at 50 RPM and 150-1200 centipoises at 10 RPM, and (ii) at least one pharmaceutically active compound selected from the group consisting of antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesic drugs.

9. The composition of Claim 8 wherein the pharmaceutically active compound is an antihistamine selected from the group consisting of chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, diphenhydramine, doxylamine, tripeleminamine, cyproheptadine, bromodiphenhydramine, phenindamine, pyrilamine and azatadine.

10. The composition of Claim 8 wherein the pharmaceutically active compound is a decongestant selected from the group consisting of pseudoephedrine HCl, phenylpropanolamine and phenylephrine.

11. The composition of Claim 10 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 10 to about 60 milligrams per 5 milliliters of the excipient base.

12. The composition of Claim 11 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 15 to about 30 milligrams per 5

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milliliters of the excipient base.

13. The composition of Claim 8 wherein the pharmaceutically active compound is an expectorant selected from the group consisting of oterpin hydrate, guaifenesin, potassium iodide, potassium citrate and potassium guaicol sulfonate.

14. The composition of Claim 13 wherein the expectorant is guaifenesin in an amount up to about 300 milligrams per 5 milliliters of the excipient base.

15. The composition of Claim 14 wherein the guaifenesin is present in an amount of about 100 to about 200 milligrams per 5 milliliters of the excipient base.

16. The composition of Claim 8 wherein the pharmaceutically active compound is an antitussive selected from the group consisting of caramiphen, dextromethorphan HBr, codeine phosphate and codeine sulfate.

17. The composition of Claim 8 wherein the antitussive is dextromethorphan HBr in an amount of between about 5 and about 20 milligrams per 5 milliliters of excipient base.

18. The composition of Claim 17 wherein the antitussive is dextromethorphan HBr in an amount of between about 10 and about 15 milligrams per 5 milliliters of excipient base.

19. The composition of Claim 8 wherein the NSAID is selected from the group consisting propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives and oxicams.

20. The composition of Claim 19 wherein the NSAID is selected from the group consisting of ibuprofen, ketoprofen

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and naproxen.

21. The composition of Claim 20 wherein ibuprofen is present in
in an amount ranging from about 50 to about 150 milligrams
per 5 milliliters of excipient base.

22. The composition of Claim 21 wherein ibuprofen is present in
in an amount ranging from about 100 to about 150 milligrams
per 5 milliliters of excipient base.

23. The composition of Claim 20 wherein naproxen is present in
in an amount ranging from about 50 to about 250 milligrams
per 5 milliliters of excipient base.

24. The composition of Claim 23 wherein naproxen is present in
in an amount ranging from about 100 to about 150 milligrams
per 5 milliliters of excipient base.

25. The composition of Claim 8 wherein the analgesic is acetaminophen.

26. The composition of Claim 25 wherein acetaminophen is present in an amount up to about 200 milligrams per 5 milliliters of the excipient base.

27. The composition of Claim 26 wherein acetaminophen is present in an amount of about 150 to about 175 milligrams per 5 milliliters of the excipient base.

28. A method for taste masking unpleasant tasting at least one pharmaceutically active compound comprising dissolving such compound into a liquid excipient base comprising

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polyethylene glycol having a molecular weight of about 950 to about 2200 and a cellulosic compound selected from the group consisting of methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, mixtures and salts thereof, the spindle viscosity of the liquid excipient bases being between about 150 and about 1000 centipoises at 50 RPM and 150-1200 centipoises at 10 RPM.

29. The method of Claim 28 wherein wherein the polyethylene glycol has a molecular weight of between 1400 and about 1600.

30. The method of Claim 28 wherein the weight ratio of polyethylene glycol and cellulosic compound is between about 100:1 and about 20:1.

31. The method of Claim 28 wherein the cellulosic compound is sodium carboxymethyl cellulose.

32. The method of Claim 31 wherein the weight ratio of polyethylene glycol and sodium carboxymethylcellulose is between about 100:1 and about 20:1.

33. The method of Claim 28 wherein the excipient base has a pH of between about 2.5 and about 5.

34. The method of Claim 28 wherein the pharmaceutically active compound is selected from the group consisting of antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesic drugs.

35. The method of Claim 28 wherein the pharmaceutically active compound is an antihistamine selected from the group

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consisting of chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, diphenhydramine, doxylamine, tripelennamine, cyproheptatine, bromodiphenhydramine, phenindamine, pyrilamine and azatadine.

36. The method of Claim 28 wherein the pharmaceutically active compound is a decongestant selected from the group consisting of pseudoephedrine HCl, phenylpropanolamine and phenylephrine.

37. The method of Claim 36 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 10 to about 60 milligrams per 5 milliliters of the excipient base.

38. The method of Claim 37 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 15 to about 30 milligrams per 5 milliliters of the excipient base.

39. The method of Claim 28 wherein the pharmaceutically active compound is an expectorant selected from the group consisting of oterpin hydrate, guaifenesin, potassium iodide, potassium citrate and potassium guaicol sulfonate.

40. The method of Claim 39 wherein the expectorant is guaifenesin in an amount up to about 300 milligrams per 5 milliliters of the excipient base.

41. The method of Claim 40 wherein the guaifenesin is present in an amount of about 100 to about 200 milligrams per 5 milliliters of the excipient base.

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42. The method of Claim 28 wherein the pharmaceutically active compound is an antitussive selected from the group consisting of caramiphen, dextromethorphan HBr, codeine phosphate and codeine sulfate.

43. The method of Claim 42 wherein the antitussive is dextromethorphan HBr in an amount of between about 5 and about 20 milligrams per 5 milliliters of excipient base.

44. The method of Claim 42 wherein the antitussive is dextromethorphan HBr in an amount of between about 10 and about 15 milligrams per 5 milliliters of excipient base.

45. The method of Claim 28 wherein the NSAID is selected from the group consisting propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives and oxicams.

46. The method of Claim 45 wherein the NSAID is selected from the group consisting of ketoprofen, ibuprofen and naproxen.

47. The method of Claim 46 wherein ibuprofen is present in in an amount ranging from about 50 to about 150 milligrams per 5 milliliters of excipient base.

48. The method of Claim 47 wherein ibuprofen is present in in an amount ranging from about 100 to about 150 milligrams per 5 milliliters of excipient base.

49. The method of Claim 46 wherein naproxen is present in in an amount ranging from about 50 to about 250 milligrams per 5 milliliters of excipient base.

50. The method of Claim 49 wherein naproxen is present in

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in an amount ranging from about 100 to about 150 milligrams per 5 milliliters of excipient base.

51. The method of Claim 28 wherein the analgesic is acetaminophen.

52. The method of Claim 51 wherein acetaminophen is present in an amount up to about 200 milligrams per 5 milliliters of the excipient base.

53. The method of Claim 51 wherein acetaminophen is present in an amount of about 150 to about 175 milligrams per 5 milliliters of the excipient base.

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/US 96/00577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 183 829 (HENRY C. CALDWELL) 2 February 1993	1-4,8, 19-24, 28-30, 34,45-50
Y	see claims 1,3 see column 2, line 16 - line 46 see column 3, line 15 - line 41 ---	9-18, 25-27, 35-44, 51-53
X	US,A,4 453 979 (DOMINICK F. DEMASI) 12 June 1984	1-6
Y	see claims 1-4 see column 2, line 66 - column 3, line 34; examples 1-4 --- -/--	28-32

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

30 May 1996

Date of mailing of the international search report

10. 06. 96

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INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 96/00577

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>EP,A,0 614 659 (TARO PHARMACEUTICAL INDUSTRIES LIMITED) 14 September 1994</p> <p>see claims 1-4 see page 4, line 1 - line 58 see examples 1-18 -----</p>	<p>9-18, 25-32, 35-44, 51-53</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00577

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5183829	02-02-93	NONE	
US-A-4453979	12-06-84	NONE	
EP-A-614659	14-09-94	AU-B- 5762894	15-09-94
		CA-A- 2118670	12-09-94
		JP-A- 7010743	13-01-95
		ZA-A- 9401002	30-09-94

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